induced specific isotyped subclass antibodies similar to those induced by IFA. No significant augmentation of fetal serum IgE was detected during this study. In addition, a boosting effect was obtained when the immunized mice were reinjected with a small antigen dose in IFA several months later. These results indicate that biodegradable MS may be a suitable vaccine delivery system/adjuvant not only for protein antigens but also for weakly immunogenic synthetic peptides. Copyright (C) 1996 Elsevier Science Ltd.

Title: DEVELOPMENT OF HIGH POTENCY UNIVERSAL DR-RESTRICTED HELPER EPITOPES BY MODIFICATION OF HIGH-AFFINITY DR-BLOCKING PEPTIDES

Author(s): ALEXANDER J; SIDNEY J; SOUTHWOOD S; RUPPERT J; OSEROFF C; MAEWAL A; SNOKE K; SERRA HM; KUBO RT; SETTE A; GREY HM

Corporate Source: CYTEL CORP,3525 JOHN HOPKINS COURT/SAN DIEGO//CA/92121

Journal: IMMUNITY, 1994, V1, N9 (DEC), P751-761

ISSN: 1074-7613

Language: ENGLISH Document Type: ARTICLE

Abstract: Pan DR-binding peptides engineered by introducing anchor residues for different DR motifs within a polyalanine backbone bound 10 of 10 DR molecules tested, with affinities, in most cases, in the nanomolar range. Because of the small methyl group exposed far T cell recognition, these peptides were poor immunogens but effective blockers of DR-restricted antigen presentation. Introduction of bulky and charged residues at positions accessible for T cell recognition yielded extremely powerful Pan DR epitope peptides (PADRE). These peptides elicited powerful responses in vitro from human peripheral blood mononuclear cells (PBMC). Because these cells also cross-react on certain mouse class II alleles, we could also demonstrate that PADRE peptides are active in vivo. In one example of their capacity to elicit T help, they were approximately 1000 times more powerful than natural T cell epitopes. We propose that PADRE peptides may be useful in the development of subunit vaccines.

Treatment of established tumors with a novel vaccine that enhances major histocompatibility class II presentation of tumor antigen.

Lin KY; Guarnieri FG; Staveley-O'Carroll KF; Levitsky HI; August JT; Pardoll DM; Wu TC

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Cancer research (UNITED STATES) Jan 1 1996, 56 (1) p21-6, ISSN 0008-5472 Journal Code: CNF

Contract/Grant No.: 5 PO1 34582-01; P50 CA62924, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Presentation of antigenic **peptides** by MHC class II molecules to CD4+ T cells is critical to the generation of antitumor immunity. In an attempt to enhance MHC class II antigen processing, we linked the sorting signals of the lysosome-associated membrane protein (LAMP-1) to the cytoplasmic/nuclear human papilloma virus (HPV-16) E7 antigen, creating a chimera (Sig/E7/LAMP-1). Previously, we found that expression of this chimera in vitro and in vivo with a recombinant vaccinia **vector targeted** E7 to endosomal and lysosomal compartments and enhanced **MHC** class **II** presentation to CD4+ T cells compared to vaccinia expressing wild-type E7. In the current study, we tested these recombinant vaccinia for in vivo protection against an E7+ tumor, TC-1, which was derived from primary epithelial cells of C57BL/6 mice cotransformed with HPV-16 E6 and E7 and c-Ha-ras oncogenes. All mice vaccinated with 1 x 10(7) plaque-forming units of wild-type E7-vaccinia showed progressive tumor growth when challenged with a tumorigenic dose of TC-1 tumor cells; in contrast, 80% of mice vaccinated with the chimeric Sig/E7/LAMP1 vaccinia remained tumor free 3 months after tumor injection. Furthermore, treatment with the Sig/E7/LAMP-1 vaccinia vaccine cured mice with small established TC-1 tumors, whereas the wild-type E7-vaccinia showed no effect on this established tumor burden. These findings point out the therapeutic limitations of recombinant vaccinia expressing unmodified tumor antigens. Further, they demonstrate that modifications that reroute a cytosolic tumor antigen to the endosomal/lysosomal compartment can profoundly improve the in vivo therapeutic potency of recombinant vaccines.

Delivery of multiple CD8 cytotoxic T cell epitopes by DNA vaccination.

Thomson SA; Sherritt MA; Medveczky J; Elliott SL; Moss DJ; Fernando GJ; Brown LE; Suhrbier A

The Cooperative Research Centre for Vaccine Technology, Queensland Institute of Medical Research, Brisbane, Australia.

Journal of immunology (UNITED STATES) Feb 15 1998, 160 (4) p1717-23, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Development of CD8 alphabeta CTL epitope-based vaccines requires an effective strategy capable of co-delivering large numbers of CTL epitopes. Here we describe a **DNA** plasmid encoding a polyepitope or "**polytope** " protein, which contained multiple contiguous minimal murine CTL epitopes. Mice vaccinated with this plasmid made MHC-restricted CTL responses to each of the epitopes, and protective CTL were demonstrated in recombinant vaccinia virus, influenza virus, and tumor challenge models. CTL responses generated by **polytope** **DNA** plasmid vaccination lasted for 1 yr, could be enhanced by co-delivering a gene for granulocyte-macrophage CSF, and appeared to be induced in the absence of CD4 T cell-mediated help. The ability to deliver large numbers of CTL epitopes using relatively small **polytope** constructs and **DNA** vaccination technology should find application in the design of human epitope-based CTL vaccines, in particular in vaccines against EBV, HIV, and certain cancers.

102 103

1, 3-8, 10, 13-14, 18-25, 27, 30-31, 35-39, 41, 44-45, 48-49, 52-54, 56, 59-60, 64

15-17, 32-34, 46-47, 50-51, 61-63

Further protection against antigenic drift of influenza virus in a ferret model by DNA vaccination.

Donnelly JJ; Friedman A; Ulmer JB; Liu MA

Department of Virus and Cell Biology, Merck Research Labroatories, West Point, PA 19486, USA.

Vaccine (ENGLAND) Jun 1997, 15 (8) p865-8, ISSN 0264-410X

Journal Code: X60

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Previously we showed that immunization of ferrets with **DNA** encoding the hemagglutinin (**HA**), nucleoprotein (**NP**), and **matrix** protein (M1) of **influenza** virus induced protective immune responses. A **DNA vaccine** encoding **HA** (from a 1991 strain), **NP** and M1 (from a 1989 strain) protected ferrets better against challenge with the antigenic drift variant A/Georgia/03/93 than did the inactivated **vaccine** from the 1992-93 **influenza** season. Here we report that the same **DNA vaccine** protected ferrets against a second, further divergent, drift variant (A/Johannesburg/33/94). Furthermore, the extent of protection provided by the **DNA vaccine** was equivalent to the homologous protection provided by an inactivated **vaccine** that exactly matched the challenge strain.

Title: Binding of malaria T cell epitopes to DR and DQ molecules in vitro correlates with immunogenicity in vivo - Identification of a universal T cell epitope in the Plasmodium falciparum circumsporozoite protein

Author(s): CalvoCalle JM; Hammer J; Sinigaglia F; Clavijo P; MoyaCastro ZR; Nardin EH (REPRINT)

Corporate Source: NYU,SCH MED, DEPT MED & MOL PARASITOL, 341 E 25TH ST/NEW YORK//NY/10010 (REPRINT); NYU,SCH MED, DEPT MED & MOL PARASITOL/NEW YORK//NY/10010; ROCHE MILANO RECERCHE,/MILAN//ITALY/

Journal: JOURNAL OF IMMUNOLOGY, 1997, V159, N3 (AUG 1), P1362-1373

ISSN: 0022-1767 Publication date: 19970801

Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814

Language: English Document Type: ARTICLE

Abstract: The efficacy of a malaria peptide vaccine would be enhanced by the inclusion of a parasite-derived **universal** T cell **epitope** to ensure that all vaccinees develop parasite-specific cellular and humoral immunity, Two circumsporozoite (CS) protein T cell epitopes, previously identified by CD4(+) T cell clones derived from Plasmodium falciparum sporozoite-immunized volunteers, were studied to determine their HLA class II binding potential, One epitope, located in amino acid (aa) 326-345 of the P, falciparum (NF54 strain) CS protein, was ''universal'' in that it could bind to multiple DR acid DQ molecules in vitro, in contrast, the second epitope, T1, which is located in the CS repeat region, tvas recognized by T cells in the context of DQ6 (DQB1*0603) and did not bind with high affinity to any of the class II molecules tested in the peptide binding assays, The in vitro patterns of peptide/HLA interactions correlated with immunogenicity in vivo, A multiple antigen peptide (MAP) containing the aa 326-345 epitope elicited responses in eight inbred strains (H*2(a,b,d,k,p,q,r,s)), while the T1 MAP was recognized by only a single haplotype, H-2(b), The combination of the universal aa 326-345 T cell epitope and the T1 repeat in a di-epitope MAP overcame the genetic restriction to the P, falciparum CS repeat region and elicited antisporozoite Ab responses in all of the MAP-immunized mice, Synthetic peptide malaria vaccines containing the aa 326-345 **universal** T cell **epitope** would be expected to elicit parasite-specific immune responses in both sporozoite-primed and naive individuals of diverse genetic backgrounds.

Title: INDUCTION OF SUSTAINED AND ELEVATED IMMUNE-RESPONSES TO WEAKLY IMMUNOGENIC SYNTHETIC MALARIAL PEPTIDES BY ENCAPSULATION IN BIODEGRADABLE POLYMER MICROSPHERES

Author(s): MEN Y; GANDER B; MERKLE HP; CORRADIN G

Corporate Source: UNIV LAUSANNE,INST BIOCHEM/CH-1066 EPALINGES//SWITZERLAND/; UNIV LAUSANNE,INST BIOCHEM/CH-1066 EPALINGES//SWITZERLAND/; ETH ZURICH,DEPT PHARM/CH-8057 ZURICH//SWITZERLAND/

Journal: VACCINE, 1996, V14, N15 (OCT), P1442-1450

ISSN: 0264-410X

Language: ENGLISH Document Type: ARTICLE

Abstract: Biodegradable microspheres (MS) based on poly (D, L-lactide) and poly (D, L-lactide-co-glycolide) have the capacity to release encapsulated antigens over defined lengths of time depending on their composition and to elicit and sustain strong and long-lasting immune responses to protein antigens. In the present study, two synthetic multiple antigenic peptides (MAP), P30B2 and (NANP)(6)P2P30, were incorporated into MS of different compositions. P30B2 and (NANP)(6)P2P30 are composed of one or two **universal** T helper **epitopes** from tetanus toxin, 947-967 (P30) and 830-843 (P2), and of a B cell epitope derived from the repeat sequence of Plasmodium berghei or Plasmodium falciparum, respectively. BALB/c mice were immunized with these two peptides in different formulations, including individual MS or mixtures of MS with various release properties, Incomplete Freund's adjuvant (IFA) or as soluble peptides. MS formulations elicited strong and sustained proliferative and antibody responses comparable to those obtained with the IFA preparations. Furthermore, MS formulations

09326108 97461118

Multi-epitope DNA vaccines.

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Immunology and cell biology (AUSTRALIA) Aug 1997, 75 (4) p402-8, ISSN 0818-9641 Journal Code: GH8

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

The evolution of vaccine strategies has seen a move from whole organisms to recombinant proteins, and further towards the ultimate in minimalist vaccinology, the epitope. The epitope-based approach is clearly compelling as only a relatively tiny, but immunologically relevant, sequence is often capable of inducing protective immunity against a large and complex pathogen. The post-reductionist era in epitope-based vaccinology has seen a quest to re-construct complexity and design vaccines containing many epitopes. The hope is that such multi-epitope vaccines might induce immunity against multiple antigenic targets, multiple strain variants, and/or even multiple pathogens. The ability of DNA vaccination to co-deliver a series of antibody and/or CD4 T cell epitopes remains largely unexplored. Successful viral vector and **DNA** -based experimental **vaccines** coding for **multiple** contiguous CD8 CTL **epitopes** have, however, recently been described. This simple CTL poly-epitope (or polytope) strategy may find application in the design of vaccines against several diseases including EBV, HIV and cancer.

12/3,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09266508 97378949

Malaria DNA vaccines in Aotus monkeys.

Gramzinski RA; Maris DC; Doolan D; Charoenvit Y; Obaldia N; Rossan R; Sedegah M; Wang R; Hobart P; Margalith M; Hoffman S

Malaria Program, Naval Medical Research Institute, Bethesda, MD, USA.

Vaccine (ENGLAND) Jun 1997, 15 (8) p913-5, ISSN 0264-410X Journal Code: X60

Languages: ENGLISH

Document type: JOURNAL ARTICLE

In preparation for the development of DNA vaccines designed to produce protective antibodies against Plasmodium falciparum antigens (Ag), we conducted studies to optimize antibody responses in Aotus monkeys after immunization with the P. yoelli circumsporozoite (CSP) DNA vaccine. We demonstrate in Aotus monkeys that an intradermal route of immunization with a PyCSP plasmid **DNA vaccine** generates antibody responses equivalent to a **multiple** antigen peptide/adjuvant based vaccine, and that these data support the use of the intradermal route for initial studies of the efficacy of DNA vaccines in inducing protective antibodies against P. falciparum antigens in Aotus monkeys.

Set	Items	Description
S1	0	UNIVERAL (3N)EPITOPE?
S2	202	UNIVERSAL (3N) EPITOPE?
S3	38	S2 AND MHC
S4	17	RD (unique items)
S5	12	S4 NOT PY>1998
S6	1096	(II OR (INVARIANT (W)CHAIN) OR (KAPPA (2N)SIGNAL?) OR INFLUENZA OR HEPATITIS OR LAMP) (4N) TARGET? (4N) (MHC OR (MAJOR(W)HISTOCOMPATABILITY(W)COMPLEX))
S7	932	S6 NOT PY>1998
S8	25	S7 (S) (VECTOR? OR CONSTRUCT? OR DNA) (S) (EPITOPE? OR PEPTIDE?)
S9	7	RD (unique items)
S10	24	((VACCINE? OR NAKED) (4N)(DNA)) (7N)(MULTIPLE (3N) (EPITOPE? OR ANTIGEN?))
S11	11	RD (unique items)
S12	8	S11 NOT PY>1998
S13	1201	POLY(W)EPITOPE OR POLYTOPE
S14	17	S13 (S)(DNA)
S15	4	RD (unique items)

Melanoma-associated antigens recognized by cytotoxic T lymphocytes.

Kirkin AF; Dzhandzhugazyan K; Zeuthen J

Department of Tumor Cell Biology, Institute of Cancer Biology, Danish Cancer Society, Copenhagen.

APMIS (DENMARK) Jul 1998, 106 (7) p665-79, ISSN 0903-4641

Journal Code: AMS

Languages: ENGLISH

The immunogenic properties of melanoma-associated antigens recognized by cytotoxic T lymphocytes.

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Department of Tumor Cell Biology, Danish Cancer Society, Copenhagen, Denmark.

Experimental and clinical immunogenetics (SWITZERLAND) 1998, 15 (1) p19-32, ISSN 0254-9670 Journal Code: AOK

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

During the last 6 years significant progress has been achieved in the identification of melanoma-associated antigens recognized by cytotoxic T lymphocytes. These antigens belong the three main groups: tumor-associated testis-specific antigens (MAGE, BAGE, GAGE and PRAME), melanocyte differentiation antigens (tyrosinase, Melan-A/MART-1, gp100, TRP-1 and TRP-2) and mutated or aberrantly expressed antigens (MUM-1, CDK4, beta-catenin, gp100-in4, p15 and N-acetylglucosaminyltransferase V). In this **review** , we have summarized the available data **concerning** the characterization of melanoma-associated antigens with focus on their immunogenic and protective properties. The development of a strong immune response against differentiation antigens is limited by the existence of tolerance against these 'self' antigens, permitting the involvement of only T cells with low affinity T cell receptors. Among the melanoma differentiation antigens, only gp100 has been shown to be a **tumor** regression **antigen** . The testis-specific antigens such as MAGE and PRAME should potentially be highly immunogenic antigens. They contain several potential HLA class I binding **epitopes** and are present only in the testes which are not accessible to the cells of the immune system due to the lack of direct contact with the immune cells and the lack of HLA class I expression on the surface of germ cells. But only 2 patients have been found who responded to these antigens in vivo, indicating their genuinely low immunogenicity. A comparison of the predicted secondary structures of these two groups of antigens (testis-specific and differentiation antigens) revealed enrichment of long alpha-helical stretches in the testis-specific antigens. We hypothesize that such highly organized structures could diminish the efficiency of the protein unfolding--a necessary step in the proteolytic cleavage by proteasomes--and, therefore, could be responsible for the low immunogenicity of these proteins. In this case, modifications decreasing the stability of these proteins might be a means to improve the immune response against these potentially therapeutically useful antigens.

An adenovirus type 5 early region 1B-encoded CTL epitope-mediating tumor eradication by CTL clones is down-modulated by an activated ras oncogene.

Toes RE; Offringa R; Blom RJ; Brandt RM; van der Eb AJ; Melief CJ; Kast WM

Department of Immunohematology and Blood Bank, University Hospital Leiden, The Netherlands.

Journal of immunology (UNITED STATES) Apr 1 1995, 154 (7) p3396-405, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Mouse embryo cells (C57BL/6, H-2b) transformed by the E1A and E1B genes of adenovirus type 5 (Ad5E1 MEC) are highly immunogenic. Previously, CTL were cloned from mice immunized with Ad5E1 MEC. These CTL clones were capable of tumor eradication in nude mice, and were directed against the Ad5E1A-encoded decapeptide **SGPSNTPPEI** , presented by the H-2Db MHC molecule. We have now generated Ad5E1 MEC containing a mutated Ad5E1A-encoded epitope. The mutant Ad5E1 MEC induce a strong CTL response when injected into immunocompetent mice. CTL clones generated against mutant Ad5E1-transformed tumor cells recognize an Ad5E1B-encoded epitope (VNIRNCCYI) in the context of H-2Db. Because this epitope is also present on wild-type Ad5E1 MEC, it is concluded that Ad5E1-transformed tumor cells express at least two CTL epitopes. Interestingly, the lysis of Ad5E1 MEC by the Ad5E1B-specific, but not by the Ad5E1A-specific, CTL clones was strongly diminished by the action of the activated ras oncogene. CTL directed against the Ad5E1B-encoded epitope were, like Ad5E1A-specific CTL, able to eradicate large established Ad5E1-induced tumors in B6 nude mice, demonstrating that CTL activity directed against different CTL epitopes expressed by the same tumor can be exploited for immunotherapy of cancer.

Title: PEPTIDE VACCINATION CAN LEAD TO ENHANCED TUMOR-GROWTH THROUGH SPECIFIC T-CELL TOLERANCE INDUCTION

Author(s): TOES REM; OFFRINGA R; BLOM RJJ; MELIEF CJM; KAST WM
Corporate Source: LEIDEN UNIV HOSP,DEPT IMMUNOHEMATOL,POB 9600/NL-2300 RC LEIDEN//NETHERLANDS/; LEIDEN UNIV HOSP,BLOOD BANK/NL-2300 RC LEIDEN//NETHERLANDS/; LOYOLA UNIV,CTR CANC,TUMOR IMMUNOL PROGRAM/MAYWOOD//IL/60153

Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1996, V93, N15 (JUL 23), P7855-7860
ISSN: 0027-8424
Language: ENGLISH Document Type: ARTICLE

Abstract: Vaccination with synthetic peptides representing cytotoxic T lymphocyte (CTL) epitopes can lead to a protective CTL-mediated immunity against tumors or viruses. We now report that vaccination with a CTL epitope derived from the human adenovirus type 5 **E1A** -region (Ad5E1A(**234** -**243**)), which can serve as a target for tumore-radicating CTL, enhances rather than inhibits the growth of Ad5E1A-expressing tumors. This adverse effect of peptide vaccination was rapidly evoked, required low doses of peptide (10 mu g), and was achieved by a mode of peptide delivery that induces protective T-cell-mediated immunity in other models. Ad5E1A-specific CTL activity could no longer be isolated from mice after injection of Ad5E1A-peptide, indicating that tolerization of Ad5E1A-specific CTL activity causes the enhanced tumor outgrowth. In contrast to peptide vaccination, immunization with adenovirus, expressing Ad5E1A, induced Ad5E1A-specific immunity and prevented the outgrowth of Ad5E1A-expressing tumors. These results show that immunization with synthetic peptides can lead to the elimination of anti-tumor CTL responses. These findings are important for the design of safe peptide-based vaccines against tumors, allogeneic organ transplants, and T-cell-mediated autoimmune diseases.

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09/316,935

5/23/98

Role of antigen-presenting cells in mediating tolerance and autoimmunity.

Garza KM; Chan SM; Suri R; Nguyen LT; Odermatt B; Schoenberger SP; Ohashi PS

Departments of Medical Biophysics and Immunology, Ontario Cancer Institute, Toronto, Canada.

Journal of experimental medicine (UNITED STATES) Jun 5 2000, 191 (11) p2021-7, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The mechanisms that determine whether receptor stimulation leads to lymphocyte tolerance versus activation remain poorly understood. We have used rat insulin promoter (RIP)-gp/P14 double-transgenic mice expressing the lymphocytic choriomeningitis virus (LCMV) glycoprotein (gp) on pancreatic beta-islet cells together with T cells expressing an LCMV-gp-specific T cell receptor to assess the requirements for the induction of autoimmunity. Our studies have shown that administration of the gp peptide gp33 leads to the activation of P14-transgenic T cells, as measured by the upregulation of activation markers and the induction of effector cytotoxic activity. This treatment also leads to expansion and deletion of P14 T cells. Despite the induction of cytotoxic T lymphocyte activity, peptide administration is not sufficient to induce diabetes. However, the administration of gp **peptide** together with an activating **anti -CD40 antibody** rapidly induces diabetes. These findings suggest that the induction of tolerance versus autoimmunity is determined by resting versus activated antigen-presenting cells.

Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues.

Wu H; Nie Y; Huse WD; Watkins JD

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Journal of molecular biology (ENGLAND) Nov 19 1999, 294 (1) p151-62, ISSN 0022-2836 Journal Code: J6V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Optimal protein function often depends on co-operative interactions between amino acid residues distant in the protein primary sequence yet spatially near one another following protein folding. For example, antibody affinity is influenced by interactions of framework residues with complementarity-determining region (CDR) residues. However, despite the abundance of antibody structural information and computational tools the humanization of rodent antibodies for clinical use often results in a significant loss of affinity. To date, antibody engineering efforts have focused either on optimizing CDR residues involved in antigen binding or on optimizing antibody framework residues that serve critical roles in preserving the conformation of CDRs. In the present study a new approach which permits the rapid identification of co-operatively interacting framework and CDR residues was used to simultaneously humanize and optimize a murine antibody directed against CD40. Specifically, a combinatorial library that examined eight potentially important framework positions concomitantly with focused CDR libraries consisting of variants containing random single amino acid mutations in the third CDR of the heavy and light chains was expressed. Multiple anti-CD40 Fab variants containing as few as one murine framework residue and displaying up to approximately 500-fold higher affinity than the initial chimeric Fab were identified. The higher affinity humanized variants demonstrated a co-operative interaction between light chain framework residue Y49 and heavy chain CDR3 residue R/K101 (coupling energy, DeltaGI=0.9 kcal/mol). Screening of combinatorial framework-CDR libraries permits identification of monoclonal antibodies (mAb) with structures optimized for function, including instances in which the antigen induces conformational changes in the mAb. Moreover, the enhanced humanized variants contain fewer murine framework residues and could not be identified by sequential in vitro humanization and affinity muturation strategies. This approach to identifying co-operatively interacting residues is not restricted to antibody-antigen interactions and consequently, may be used broadly to gain insight into protein structure-function relationships, including proteins that serve as

catalysts. Copyright 1999 Academic Press.

Title: CD40-CD40 LIGAND INTERACTIONS IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND MULTIPLE-SCLEROSIS

Author(s): GERRITSE K; LAMAN JD; NOELLE RJ; ARUFFO A; LEDBETTER JA; BOERSMA WJA; CLAASSEN E

Corporate Source: TNO PREVENT & HLTH,DIV INFECT DIS & IMMUNOL,POB2215/2301 CE LEIDEN//NETHERLANDS/; TNO PREVENT & HLTH,DIV INFECT DIS & IMMUNOL/2301 CE LEIDEN//NETHERLANDS/; ERASMUS UNIV ROTTERDAM,DEPT IMMUNOL/3015 GE ROTTERDAM//NETHERLANDS/; DARTMOUTH COLL SCH MED,DEPT MICROBIOL/LEBANON//NH/03756; BRISTOL MYERS SQUIBB PHARMACEUT RES INST/SEATTLE//WA/98121

Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1996, V93, N6 (MAR 19), P2499-2504

ISSN: 0027-8424

Language: ENGLISH Document Type: ARTICLE

Abstract: We investigated the role of CD40-CD40 ligand (CD40L) interactions in multiple sclerosis (MS) and experimental allergic encephalomyelitis (EAE). Activated helper T cells expressing CD40L (gp39) surface protein were found in MS patient brain sections, but not in brain tissue sections of normal controls or patients with other neurological diseases. CD40L-positive cells were co-localized with CD40-bearing cells in active lesions (perivascular infiltrates). Most of these CD40 bearing cells proved to be of the monocytic lineage (macrophages or microglial cells), and relatively few were B cells. To functionally evaluate CD40-CD40L interactions, EAE was elicited in mice by means of proteolipid-peptide immunization. Treatment with anti-CD40L monoclonal antibody completely prevented the development of disease. Furthermore, administration of anti-CD40L monoclonal antibody, even after disease onset, shortly before maximum disability score was reached led to dramatic disease reduction. The presence of helper T cells expressing CD40L in brain tissue of MS patients and EAE animals, together with the functional evidence provided by successful experimental prevention and therapy in an animal model, indicates that blockade of CD40-CD40L-mediated cellular interactions may be a method for interference in active MS.

03513433 Genuine Article#: PJ300 Number of References: 22

Title: VASOACTIVE-INTESTINAL-PEPTIDE SPECIFICALLY INDUCES HUMAN IGA1 AND IGA2 PRODUCTION

Author(s): KIMATA H; FUJIMOTO M

Corporate Source: KYOTO UNIV HOSP,FAC MED,DEPT PEDIAT,SAKYO KU,54KAWAHARA CHO/KYOTO 606//JAPAN/

Journal: EUROPEAN JOURNAL OF IMMUNOLOGY, 1994, V24, N9 (SEP), P2262-2265

ISSN: 0014-2980

Language: ENGLISH Document Type: NOTE

Abstract: The effects of vasoactive intestinal peptide (VIP) on human IgA1 and IgA2 production were studied. In unfractionated small resting B cells stimulated with anti-CD40 monoclonal antibody (mAb), VIP induced IgA1 and IgA2 production without affecting the production of IgG1, IgG2, IgG3, IgG4, IgM, or IgE. When small B cells were separated into sIgA1(+), sIgA2(+), sIgA1(-) and sIgA2(-) B cells, anti-CD40 mAb plus VIP induced IgA1 and IgA2 production by surface IgA1(sIgA1(-)) and sIgA2(-) B cells, respectively, while having no effect on sIgA1(+) and sIgA2(+) B cells. This induction by VIP was specific, since anti-CD40 mAb plus other neuropeptides, i.e., somatostatin or substance P, had no effect, and moreover, the induction was specifically blocked by a VIP antagonist. Further, anti-CD40 mAb plus various cytokines, including interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, transforming growth factor-beta, low molecular weight B cell growth factor, and interferon-gamma, did not induce IgA1 and IgA2 production by sIgA1(-) and sIgA2(-) B cells, respectively. These results indicate that in the presence of anti-CD40 mAb, VIP induces IgA1 and IgA2 production by isotype switching.

The anti- CD40 antibody **G28-5 has potent antitumor activity in vivo**

when administered as either an IgG or sFv (Meeting abstract).

Schreiber GJ; Francisco JA; Ledbetter JA; Walls MA; Harris L; Siegall CB

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121 USA

Proc Annu Meet Am Assoc Cancer Res; 38:A562 1997 ISSN 0197-016X

Languages: ENGLISH

Document Type: MEETING ABSTRACTS

The CD40 antigen is expressed on a variety of human hematological malignancies of B-cell lineage, including non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's disease, some leukemias, and certain carcinomas. The monoclonal antibody (mAb), G28-5, a murine IgG1, binds to CD40 with a high affinity, (0.2 nM). The antitumor activity of the mAb, its F(ab')2 fragment, and its single chain sFv form, were tested in vitro and in vivo. Both the intact mAb and the sFv inhibited the growth of lymphoma cell lines in vitro in a dose-dependent and cell density-specific fashion. The in vivo antitumor efficacy of the mAb, the F(ab')2 fragment, and the sFv were examined in SCID mice bearing disseminated Ramos Burkitt's lymphoma cells. **Treatment** was initiated either 1,5,9, or 13 days post iv injection of 1 x 10(6) Ramos cells. Untreated xenografted mice succumbed to disease as manifested by hindleg paralysis induced by deposits of **tumor** cells on the spinal column within 30 days of iv **tumor** injection. The IgG, (0.4 mg/kg, q4dx5) was highly efficacious in preventing the onset of disease when administered up to 9 days after **tumor** cell implantation. Mice **treated** with a comparable amount of the G28-5 F(ab')2 fragment had no antitumor effect. Interestingly, administration of G28-5 sFv resulted in a significant delay of symptoms even after the xenografts were allowed to establish for five days prior to **treatment** . Due to the antitumor activity of the IgG and sFv, humanized versions of G28-5 have been prepared and are being evaluated alone and in combination with standard chemotherapeutic agents.

Differential in vitro and in vivo antitumor effects mediated by anti-CD40 **and anti-CD20 monoclonal antibodies against human B-cell lymphomas.**

Funakoshi S; Longo DL; Murphy WJ

Laboratory of Leukocyte Biology, National Cancer Institute-Frederick Cancer Research and Development Center, MD 21702-1201, USA.

Journal of immunotherapy with emphasis on tumor immunology (UNITED STATES) Mar 1996, 19 (2) p93-101, ISSN 1067-5582 Journal Code: BZH

Languages: ENGLISH

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The antitumor effects of **CD40** and CD20 monoclonal **antibodies** (mAbs) were compared on various human B-cell lymphomas by using both in vitro and in vivo assays. **Anti -CD40** directly inhibited the proliferation of human B-cell lymphomas in vitro, whereas anti-CD20 exerted no inhibitory effects

S26	24	((ANTI(W)CD40) OR (ANTIBOD? (3N) CD40)) (8N) PEPTIDE?
S27	10	RD (unique items)
S28	3078	(ANTI(W)CD40) OR (ANTIBOD? (3N) CD40)
S29	152	S28 AND PEPTIDE?
S30	63	RD (unique items)
S31	44	S30 NOT PY>1998
S32	42	S31 NOT S27
S33	866	S28 AND (CANCER? OR TUMOR? OR TUMOUR?)
S34	319	S33 AND (TREAT? OR IMMUNIZ? OR THERAP? OR VACCIN?)
S35	197	S34 NOT PY>1998
S36	85	RD (unique items)